REMARKS

Claims 13, 14, 16-21, 31, 32, and 43-54 are pending. With this Amendment, claim 50 has been cancelled without prejudice to Applicants' right to pursue the cancelled claim in this or a related application(s). Applicants assert that the cancellation of claim 50 obviates the Examiner's objection to claim 50 for failing to limit the subject matter of a previous claim.

Additionally, in consideration of the Examiner's suggestions at the Interview (discussed below), claims 13 and 21 have been amended and new claims 55-61 have been added to better reflect the invention, *i.e*, the discovery that tissue protective molecules signal through the tissue protective cytokine receptor complex. Exemplary support for the amendment to claims 13 and 21 can be found in paragraphs [0037] and [00259]-[00263] and in Figure 7 of the specification as filed. Exemplary support for new claim 55 can found in paragraphs [0087]-[0093] of the specification as filed. Exemplary support for new claim 56 can be found in paragraph [0094] of the specification as filed. Exemplary support for new claims 57 and 60 can found in paragraphs [00259]-[00263] of the specification as filed. Exemplary support for new claims 58 and 59 can be found in paragraph [0095] of the specification as filed. Exemplary support for new claim 61 can found in paragraphs [0078], [00139], [00140], and [00155]-[00158] of the specification as filed. Therefore, Applicants assert that no new matter has been introduced by the amendments to the claims or by the newly added claims. Upon entry of this Amendment, claims 13, 14, 16-21, 31, 32, 43-49 and 51-61 will be pending.

Applicants believe the rejection for lack of enablement has been overcome in view of the amendments to claims 13 and 21 and the arguments set forth below.

I. Summary Of The Substance Of The Interview

Applicants thank Primary Examiner Ruixiang Li, for the courtesies extended during the interview of February 5, 2009 at the United States Patent and Trademark Office ("the Interview"). Present at the Interview were Drs. Anthony Cerami and Michael Brines, two of the inventors of the instant application, Frederick J. Hamble, Esq., of Warren Pharmaceuticals, Inc., and Applicants' representative Eileen E. Falvey.

During the Interview, the outstanding rejections made in the Office Action mailed August 19, 2008 (the "Office Action") were discussed and suggestions were made to overcome the rejection. This Amendment, and the remarks herein, reflect the discussion during the Interview.

II. The Rejections For Lack Of Enablement Should Be Withdrawn

The Examiner has rejected 13, 14, 16-21, 31, 32, and 43-54 under 35 U.S.C. § 112, first paragraph, as lacking enablement. Claim 50 has been cancelled herein, obviating the Examiner's rejection of this claim. In particular, the Examiner alleges that while being enabling for a method of using an EPO receptor and a βc receptor complex in screening assays to identify a compound that inhibits apoptosis in cardiomyocytes, the specification does not reasonably provide enablement for a method of identifying a compound that exhibits tissue protective activity, wherein the tissue protective activity inhibits damage/death of tissue or organ, or for cell types other than cardiomyocytes.

For at least the reasons set forth below, Applicants respectfully disagree with the Examiner.

A. The Legal Standard

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). In fact, well known subject matter is preferably omitted. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) ("a patent need not teach, and preferably omits, what is well known in the art."). Further, one skilled in the art is presumed to use the information available to him in attempting to make or use the claimed invention. *See Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990) ("A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation."). These enablement rules preclude the need for the patent Applicant to "set forth every minute detail regarding the invention." *Phillips Petroleum Co. v. United States Steel Corp.*, 673 F. Supp. 1278, 1291 (D. Del. 1991); *see also DeGeorge v. Bernier*, 768 F.2d 1318, 1323 (Fed. Cir. 1985).

Undue experimentation is experimentation that would require a level of ingenuity *beyond* what is expected from one of ordinary skill in the field. *Fields v. Conover,* 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174. The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands,* 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the breadth of the claims, the level of predictability in the art, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature, and the level of skill in the art. Moreover, the test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, so long as it is merely routine. *Id.*

Further, while the predictability of the *art* can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the *result* of an experiment is *not* a consideration. Indeed, the Court of Custom and Patent Appeals in *In re Angstadt,* has specifically cautioned that the unpredictability of the result of an experiment is *not* a basis to conclude that the amount of experimentation is undue. In particular, in an unpredictable art it is not necessary for an inventor to disclose a test with every *species* covered by a claim, as it would force an inventor seeking adequate patent protection to carry out a prohibitive number of experiments – and discourage inventors from filing applications in an unpredictable area. *In re Angstadt,* 190 U.S.P.Q. 214 (C.C.P.A. 1976).

B. <u>The Claimed Invention Is Fully Enabled</u>

The instantly pending claims are separately drawn to screening methods for (i) identifying a compound that modulates a tissue protective activity; and (ii) identifying a compound that modulates the activity of a tissue protective cytokine receptor complex comprising an erythropoietin receptor and a βc receptor, such that a compound that has the ability to inhibit apoptosis is identified as a compound that modulates a tissue protective activity or modulates the activity of a tissue protective cytokine receptor complex comprising an erythropoietin receptor and a βc receptor.

As discussed above, the Examiner acknowledges that the specification is enabling for the identification of compounds that modulate a tissue protective activity, *i.e.*, inhibit apoptosis (cell death), in cardiomyocytes (*see* Example 5 at page 106 of the specification as filed). The gravamen of the Examiner's rejection of the pending claims is based on the Examiner's contention that it would be unpredictable whether a compound identified using the claimed screening methods exhibits a tissue protective activity, particularly when said tissue protective activity inhibits the damage/death of a tissue or organ.

By this amendment, claims 13 and 21 have been amended to include a step of assaying the compound for the ability to inhibit apoptosis. Because inhibition of apoptosis is the underlying mechanism of tissue protective activity, a compound that inhibits apoptosis necessarily defines a compound that has tissue protective activity. As such, the claims, as amended, are clearly enabling for a method of identifying a compound that exhibits tissue protective activity wherein the tissue protective activity inhibits damage/death of tissue or organs.

Moreover, the scope of enablement is not limited to cardiomyocytes. Applicants point out that the cardiomyocytes used in Example 5 were isolated directly from the hearts of mice. Applicants assert that one of skill in the art knows that tissues are merely ensembles of cells from the same origin that carry out a specific function and that organs are formed by the functional groupings of various tissues. Thus, Applicants assert that one of skill in the art would readily recognize that a compound that inhibits the cell death of cardiomyocytes not only would render an effect on isolated cardiomyocyte cells, but also would inhibit the cell death of heart tissue (which comprises cardiomyocytes) and, as a consequence, inhibit death of the heart itself (an organ). As such, Applicants assert that this *is* an example of how a compound identified in a screening method provided herein could be assayed for a tissue protective activity, wherein said tissue protective activity inhibits the damage/death of a tissue or organ.

Furthermore, Applicants assert that the specification is replete with direction for testing compounds identified using the claimed screening methods for tissue protective activity (*see* Section 5.3 at page 53 of the specification as filed). Section 5.3.1 of the specification describes *in vivo* biological assays for determining whether a compound exhibits a tissue protective activity, including detection of proteins known to be upregulated by tissue protective activity

(*e.g.*, nucleolin, neuroglobin, and cytoglobin) and well-established animal models that could be used to test the efficacy of an identified compound (*e.g.*, the protection against the onset of Acute Experimental Allergic Encephalomyelitis in Lewis rats; restoration or protection from diminished cognitive function in mice after receiving brain trauma; and protection from induced retinal ischemia in mice). Sections 5.3.2 to 5.3.5 of the specification provide well-established *in vitro* assays which one of skill in the art could use to determine whether an identified compound exhibits tissue protective activity in the cell type of their choice. Section 5.3.5.1 of the specification describes the use of genetically engineered knock-out mice that lack the βc receptor and describes methods of using these mice in conjunction with wild-type mice (which express the βc receptor) for determining whether a compound has tissue protective activity. As described in the specification, one of skill in the art could administer an agent known to cause tissue or organ damage to the knock-out and wild-type mice followed by administration of a compound identified in the claimed screening methods. If a tissue protective activity were observed in the wild-type animals, then one of skill in the art would understand that said compound indeed possesses a tissue protective activity.

Applicants assert that the methods taught in Section 5.3 are routine and art-accepted and clearly provide those skilled in the art with a means for identifying whether a given compound exhibits a tissue protective activity, wherein said tissue protective activity inhibits the damage/death of a cell, tissue, or organ. As such, it would *not* require undue experimentation by one skilled in the art to practice the claimed invention.

Finally, as further evidence of the enabling nature of the instant specification, Applicants present herein post-filing publications Brines et al., 2004, PNAS 101:14907-14912 ("Brines"); Fiordaliso et al., 2005, PNAS 102:2046-2051 ("Fiordaliso"); and Erbayaktar et al., 2006, Mol. Med. 12:74-80 ("Erbayaktar"), all of which, by following the teaching of the instant specification, identified whether or not a compound had tissue protective activity, wherein said tissue protective activity inhibits the damage/death of a cell, tissue, or organ.

Brines induced spinal cord injury in wild-type mice expressing the βc receptor and mice engineered to lack the βc receptor (*see* Brines at page 14910, left column). Immediately following the injury, both sets of mice were administered carbamylated EPO (cEPO), which Brines showed to have a high affinity for the tissue protective cytokine receptor complex (*see*

Brines at page 14909, right column). Brines reports that the wild-type mice recovered completely four weeks following cEPO treatment whereas the βc receptor knock-out mice exhibited no difference in motor function six weeks after treatment.

Fiordaliso demonstrates that, similar to the effects of EPO on murine cardiomyocytes described in Example 5 of the instant specification, cEPO inhibits apoptosis of rat cardiomyocytes (*see* Fiordaliso at 2047, right column to page 2048, left column). Fiordaliso further demonstrates that cEPO exhibits this tissue protective activity *in vivo*. Using a rat model of myocardial infarction with reperfusion, Fiordaliso reports that cEPO-treated rats had an attenuated loss of cardiac myocytes and prevented compensatory hypertrophy as compared to their non-treated counterparts (*see* Fiordaliso at page 2048, left column to page 2050, left column).

Erbayaktar reports that when given to mice prior to and following a necrotizing dose of gamma irradiation, cEPO significantly reduces the acute behavioral abnormalities and the extent of necrosis that typically follow high-dose radiation injury (*see* Erbayaktar at page 75, middle column).

Applicants assert that each of the foregoing references clearly demonstrates that the tissue protective cytokine receptor complex is involved in signaling in excitable tissues, of which, the cardiomyocyte assay described in the specification, is an example.

In view of the foregoing remarks, Applicants respectfully submit that at the time the application was filed, one of skill in the art would *not* have required undue experimentation to practice the claimed invention. As such, Applicants request that the rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement, be withdrawn.

III. The Rejections For Obviousness Should Be Withdrawn

Claims 13, 14, 17, 19, 20, 48, 49, and 51-54 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Jubinsky, *et al.* (Blood 90:1867-1873, 1997, "Jubinsky") in view of Mercury™ Pathway Profiling System User Manual (Clontech, March 2, 2001, "Mercury"). The Examiner alleges that: (i) Jubinsky teaches a functional complex comprising the EPO receptor (EPO-R) and a βc receptor in murine Ba/F3 cells that were transfected with either the murine EPO-R or EPO-R/βc, a functional role for the βc receptor in the EPO-dependent proliferation of Ba/F3 cells expressing the EPO-R, and a method for identifying the effect of sense, antisense,

and nonsense oligodeoxynucleotides to βc on EPO-dependent proliferation and β-globin expression in Ba/F3 cells; and (ii) Mercury teaches various reporter genes and vectors containing a promoter and response element which control the transcription of the reporter genes and an assay for screening a compound for its effect based upon the reporter gene activity. The Examiner asserts that it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Jubinsky to include the reporter system of Mercury with a reasonable expectation of success, and motivated to do so because the Mercury system is ideal for use with membrane receptors.

Claims 13, 16-18, 21, 43-48, and 50-54 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Jubinsky in view of Trueheart *et al.* (U.S. Patent No: 6,159,705, December 12, 2000, "Trueheart"). Claim 50 has been cancelled herein, obviating the Examiner's rejection of this claim. The Examiner alleges that Trueheart teaches rapid, reliable, and effective assays for screening and identifying pharmaceutically effective compounds that specifically interact with and modulate the activity of a heterologous receptor and that the cells used in the assays provided by Trueheart may be of prokaryotic or eukaryotic origin and may include yeast cells. The Examiner asserts that it would have been obvious to one having skill in the art to combine the method of Jubinsky to functionally express the EPO-R and βc receptor in a prokaryotic cell, such as a yeast cell or a human cell, in order to screen various compounds using a reporter gene taught by Trueheart, in order to identify a compound that modulates a tissue protective productive activity of the EPO-R/βc receptor complex with a reasonable expectation of success. The Examiner contends that one would have been motivated to do so because the assay system of Trueheart provides a rapid, reliable, and effective assay for screening and identifying effectors of a receptor protein or complex thereof.

For at least the reasons set forth below, Applicants respectfully disagree with the Examiner.

A. <u>The Legal Standard</u>

A finding of obviousness requires that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. §103(a).

In its recent decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), the Supreme Court stated that the following factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734, 82 USPQ2d at 1388 quoting *Graham*, 383 U.S. at 17-18, 14 USPQ at 467. The Supreme Court affirmed that to find obviousness, it is "*important to identify a reason* that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, 127 S.Ct. at 1741, 82 USPQ2d at 1396, emphasis added. Moreover, the relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988). In addition, evidence of unexpected or unobvious results is objective evidence of nonobviousness, and may be used to rebut a *prima facie* case of obviousness. *In re Wagner*, 371 F.2d 877 (C.C.P.A. 1967); M.P.E.P. § 716.02.

Finally, in making a determination of obviousness, one must consider the prior art from the perspective of a person having ordinary skill in the art at the time the invention was made. "Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999), citing to *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983). The *KSR* Court, citing *Graham,* upheld the principle of *avoiding hindsight bias* and cautioned courts to *guard against reading into the prior art the teachings of the invention in issue*. 127 S.Ct. at 1742, 82 USPQ at 1397:

> A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. See *Graham*, 383 U.S., at 36, 86 S.Ct. 684 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "'guard against slipping into the use of hindsight'" (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412 (C.A.6 1964))).

B. The Claimed Invention is Nonobvious over Jubinsky Combined With Mercury Or Trueheart

Applicants again assert that, at the filing date of the instant application, one of skill in the art would have had no discernible reason for combining Jubinsky with either Mercury or Trueheart because they would have had no reasonable expectation of successfully arriving at the claimed method for identifying a compound with tissue protective activity.

In the Amendment filed July 28, 2008, Applicants pointed out to the Examiner that Jubinsky failed to demonstrate any functional role for βc in the EpoR proliferative pathway *in vivo* (*see* page 10). In particular, Applicants referred to a portion of text in Jubinsky stating that "animals deficient in either βc or βIL-3 have not been reported to have impaired erythropoiesis." (Jubinsky at page 1872, citing to Nishinakamura et al., Immunity 2:211, 1995 ("Nishinakamura") and Stanley et al., Proc. Natl. Acad. Sci. 91:5592, 1994 ("Stanley")). Applicants went on to discuss how Jubinsky attempted to reconcile his findings with those of Nishinakamura and Stanley, by raising the possibility that EPO interacts with the non-disrupted β chain in these mice (Jubinsky, at page 1872). Jubinsky concluded: "[t]herefore, mice deficient in *both* βc and βIL-3 will *need to be assessed*, as these two chains have functional redundancy. *Such mice would be more analogous to our studies...*" (*Id.*, emphasis added).

In the Office Action, the Examiner has dismissed these facts as irrelevant, due to the fact that the instant claims are drawn to an *in vitro* screening method for a compound with tissue protective activity (*see* page 11 of the Office Action). Applicants respectfully disagree with the Examiner and assert that Jubinsky's discussion of Nishinakamura and Stanley is *highly relevant* as it relates to the mindset of the skilled artisan based on Jubinsky's data. Applicants assert that Jubinsky's statements clearly illustrate that Jubinsky himself was not sure whether his *in vitro* findings were of particular relevance in view of existing physiological data (*i.e.*, the studies of Nishinakamura and Stanley).

In the July 28, 2008 Amendment, at page 11, Applicants then pointed out to the Examiner that subsequent to the Jubinsky publication, mice lacking *both* the βc and βIL-3 receptor genes -- *the very mice that Jubinsky had suggested should be studied* -- were indeed produced by Scott et al., 2000, Blood 96:1588-1590 ("Scott"), and that *no effect* of βc on EPO responsiveness was detected in these mice (*see* Scott at page 1590). As discussed in the July 28, 2008 Amendment,

Scott concluded that the results of studies performed in cell lines, such as that of Jubinsky, did *not* have physiological significance because they could not be supported, and in fact they were disproved, by primary cell data, stating, at page 1590:

> [T]he demonstration of direct physical interaction involving the βc/βIL-3 receptor systems in cell lines did not extrapolate to an interaction of physiological significance in primary hematopoietic cells. This result is important for interpreting the significance of biochemical interactions between receptor molecules, particularly in studies in which cell lines are employed.

In response to the clear evidence provided by Scott, showing Jubinsky's findings to lack significance, the Examiner argues that "multiple lines of evidence support the view that the βc chain functionally associates with the EPO-R and forms a EPO-R+βc [receptor] complex," citing to Hanazono et al., 1995, Biochem. Biophys. Res. Comm. 208:1060-1066 ("Hanazono") and D'Andrea et al., 1998, J. Clin. Invest. 102:1951-1960 ("D'Andrea")(*see* page 11 of the Office Action).

First, Applicants point out that both of the references the Examiner has cited were published *before* Scott. Second, Applicants assert that neither of these references support the Examiner's argument.

Hanazono demonstrates that EPO induces tyrosine phosphorylation of the β chain of the GM-CSF receptor (*see* Hanazono at page 1061). Hanazono does not conclude that this is because of a functional relationship between the EPO and βc receptors nor does Hanazono speculate that these receptors might complex. In fact, Hanazono explicitly states that "[t]he β chain is a component of the GM-CSF receptor *but not* the EPO receptor" (*see* Hanazono at the top of page 1065; emphasis added). Clearly, Hanazono directly contradicts the Examiner's argument that, at the time the instant application was filed, the prevailing view was that the βc chain functionally associates with the EPO-R and forms a EPO-R+ βc receptor complex.

D'Andrea demonstrates that splenic erythroid progenitor cells (CFU-E) taken from transgenic mice that express the human βc receptor grow in response to EPO, whereas littermate controls lacking the human βc receptor do not (*see* D'Andrea at page 1955, right column to page 1956, left column). Citing to Jubinsky, D'Andrea speculates that their findings might be due to a direct physical interaction between the human βc receptor and the murine EPO receptor (*see* D'Andrea at page 1958, bottom of the left column). D'Andrea then acknowledged that his

speculated association between the receptors required validation, stating, at page 1958, right column:

> A more definitive demonstration of a functional role for βc in non-myeloid lineages awaits the generation of animals lacking functional βc and βIL-3. Animals deficient in either βc or βIL-3 have not been shown to have impaired erythropoiesis or megakaryopoiesis (53, 54) [D'Andrea cites Nishinakamura and Stanley]; however, these animals will have one of the β subunits intact and this may still allow a functional interaction with EPO-R to occur.

Applicants point out that this is *exactly* the same study that Jubinsky proposed for validation of his studies. Thus, Applicants assert that D'Andrea clearly *does not* conclude a functional relationship between the EPO and βc receptors, but merely speculates that one might exist and, like Jubinsky, acknowledges that further experiments need to be undertaken to determine the potential physiological relevance of his findings. As discussed, *supra*, Scott carried out the studies proposed by Jubinsky and D'Andrea, and did not uncover a physiological role for the βc receptor.

The Examiner further argues that Scott "does not rule out a functional role of βc because it is well known that EPO binds to EPO receptor homodimers and promote[s] cell proliferation, which may well explain the observed results of Scott" (*see* Office Action, page 12). Although Applicants do not disagree with the Examiner that EPO is known to bind EPO homodimers, and could thus explain why Scott observed a response to EPO, Applicants point out that Jubinsky is concerned only with EPO-induced cell growth and the potential role of the βc receptor in the EPO receptor proliferative signaling pathway (*see* Jubinsky at page 1871, right column). Indeed, Jubinsky does not teach or suggest that compounds other than EPO might modulate the EPO-R/βc receptor complex. Thus, in demonstrating that βc does *not* play a role in the EPO receptor proliferative signaling pathway, Scott tears down the very foundation of Jubinsky's study. Moreover, Applicants reiterate that Jubinsky himself called for further experimentation to validate his studies. Experimentation that was performed by Scott. Thus, in view of Scott, Jubinsky, clearly representative of one of skill in the art, would have determined that his studies lacked significance. As such, Applicants assert that it is only via hindsight analysis that the Examiner downplays the findings of Scott and reaches the conclusion that, even after the

publication of Scott, one of skill in the art would use Jubinsky to come up with the instantly claimed methods. However, such analysis, of course, is inappropriate.

Finally, Applicants respectfully point out that the Examiner seems to have completely dismissed the fact that Jubinsky specifically called for the study performed by Scott as a means to validate his results. The Examiner states that Jubinsky "explain[s] why both Nishinakamura and Stanley saw no change in the test animals' responsiveness to EPO despite the lack of either [the] βc or βIL-3 receptor gene" (*see* page 14 of the Office Action). However, this is simply not the case. Jubinsky does not, in fact, explain anything in this regard. Jubinsky attempts to reconcile his study with previous studies that detract from his results, *i.e.*, Nishinakamura and Stanley. Jubinsky goes on to propose a study, *i.e.*, that performed by Scott, that Jubinsky believes will validate his results in light of Nishinakamura's and Stanley's findings. However, Scott's study ultimately found that the results reported by Jubinsky lacked significance. Thus, Applicants assert that, one of skill in the art, when considering the study suggested by Jubinsky (and also by D'Andrea) and ultimately undertaken by Scott, would have taken Jubinsky's results to lack significance.

As such, one of skill in the art would have had *no reasonable expectation of success* at arriving at the instantly claimed invention by combining Jubinsky with Mercury or Trueheart and thus would have had *no reason* to combine these references.

Applicants reiterate that it was not until Applicants' discovery that the hematological activity of EPO could be separated from its tissue protective activity described in the instant application, that the claimed methods for identifying compounds that modulate tissue protective activity using the tissue protective complex comprising an EPO receptor and a βc receptor were imaginable.

In addition to the reasons discussed above, claims 13, 14, 17, 19, 20, 48, 49, and 51-54, and newly added claims 55-61, are non-obvious over Jubinsky combined with Mercury or Trueheart, for the reason that neither Jubinsky, Mercury nor Trueheart, either alone or taken together, teach or suggest a method for identifying a compound that has tissue protective activity or a method for identifying a compound that modulates the activity of a tissue protective cytokine receptor complex comprising a step of assaying the test compound for the ability to inhibit apoptosis such that a test compound that binds to the tissue protective cytokine receptor

complex and inhibits apoptosis is identified as a compound that has tissue protective activity or a compound that modulates the activity of a tissue protective cytokine receptor complex. In addition, new claims 84-92 are not obvious over Jubinsky combined with Mercury or Trueheart for the reason that these claims are drawn to specific assays for identifying whether or not a compound has the ability to inhibit apoptosis, which assays are not taught or suggested by Jubinsky, Mercury or Trueheart. Therefore, Applicants assert that Jubinsky, taken alone or combined with Mercury or Trueheart, does teach or suggest the subject matter of the instantly pending claims.

In view of the arguments above, Applicants assert that it would not have been obvious to one of ordinary skill in the art to combine the teachings of Jubinsky with either Mercury or Trueheart to identify a compound that modulates a tissue protective activity of the EPO-R/βc complex. Therefore, Applicants respectfully request that the rejection of claims under 35 U.S.C. § 103(a), for obviousness, be withdrawn.

CONCLUSION

Applicants respectfully request entry of the amendments and consideration of remarks above. Withdrawal of all the rejections and an allowance are earnestly sought.

Respectfully submitted,

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